chloromethylene)anilines with ethylenediamine in ethyl acetate in the presence of triethylamine. The *N*-(dichloromethylene)anilines were prepared from the formamides with thionyl chloride in sulfuryl chloride. The formamides became available by formylation of the corresponding anilines. For information on the general synthesis of substituted 2-(phenylimino)imidazolidines, see ref 15, 17, and 19.

Compounds 2 and 3, as well as clonidine, were studied for their ability to decrease mean arterial pressure in pentobarbital-anesthetized normotensive rats.[12,16] Upon intravenous administration, clonidine (1–10 μg/kg), 2 (0.3–6 μg/kg), and 3 (1–30 μg/kg) elicited the common biphasic response on arterial pressure. After a short-lasting hypertensive effect, a more persistent fall in pressure was obtained. When the maximal decrease in mean arterial pressure (percent of preinjection value) was plotted against log dose (moles/kilogram), log dose–depressor response curves were constructed, from which the -log doses for 20% decreases, pC_{20}, were calculated. As reported in Table I, compound 2 was found to be approximately 3 times more potent than clonidine in decreasing mean arterial pressure of anesthetized normotensive rats by 20% after intravenous injection. Derivative 3 had hypotensive activity comparable to clonidine.

Acute central hypotensive effectiveness of the congeners was determined by infusing them via the left vertebral artery of chloralose-anesthetized cats.[13] Accordingly, clonidine (0.1–2 μg/kg), 2 (0.1–1 μg/kg), and 3 (0.5–10 μg/kg) immediately caused a sharp fall in arterial pressure without a preceding hypertensive effect. Log dose–response curves were constructed for the maximal decrease in mean arterial pressure (percent of initial value), and -log dose for 20% decrease, pC_{20}, was calculated. As listed in Table I, the 2,3,6-trichloro-substituted molecule 2 was 3 times more effective than clonidine, whereas the 2,3-dichloro-6-methyl derivative 3 was less active than clonidine.

The results show that the introduction of a third substituent at the meta position of the phenyl ring of 2,6-disubstituted clonidine-like imidazolidines does not necessarily hamper hypotensive activity following systemic application, as has been generally observed for all 2,4,6-trisubstituted 2-(phenylimino)imidazolidines.[7,11–15,20] The para position allows only for small substituents, like OH and NH_2, for high hypotensive activity.[14,15,20] However, these groups profoundly affect lipophilicity, so that the increase in activity at the receptor level is overwhelmed by poor penetration into the central nervous system, resulting in moderate overall hypotensive potency. To our knowledge, compound 2 is the most effective hypotensive clonidine-like imidazolidine reported. The increase in hypotensive activity of compound 2 over clonidine may be due to more favorable penetration abilities of the former, as illustrated by its log P' value (Table I), which is closer to the ideal value of 2.16 determined for this series of drugs.[21]

In summary, members of 2,3,6-trisubstituted clonidine-like 2-(phenylimino)imidazolidines show potential for pronounced hypotensive activity following systemic administration. This new class of derivatives needs further exploration with respect to their substituent allowance on the phenyl ring.

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Sparsophenicol: A New Synthetic Hybrid Antibiotic Inhibiting Ribosomal Peptide Synthesis

Sir:

Recently, we suggested[1] that the biological activity of chloramphenicol (1a)—an antibiotic inhibiting procaryotic ribosomal protein synthesis—can be explained in terms of retro-inverso relationship[2] to the amino acid moiety of another strong inhibitor puromycin.[3] It should be possible to extend this hypothesis to other antibiotics, for example, sparsomycin,[4] that carry an acylamido function attached to the asymmetric (D) carbon of the substituted propanol moiety and interfere with ribosomal protein synthesis. This approach would lead to novel synthetic antibiotics by a simple interchange of the relevant *N*-acyl residues.

We now report on the first case[5] of such a hybrid antibiotic (1b) derived from a combination of chloramphenicol (1a) and sparsomycin (1c)—hence, the suggested name sparsophenicol—which is indeed a strong inhibitor of ribosomal peptide synthesis.

β-(*E*)-1,2,3,4-Tetrahydro-6-methyl-2,4-dioxo-5-pyrimidineacrylic acid[6] (2b; 0.5 g, 2.5 mmol) was converted to the corresponding mixed anhydride by reaction with triethylamine (0.35 mL, 2.5 mmol) and isobutyl chloroformate (0.32 mL, 2.5 mmol) in acetonitrile (20 mL).[7] A solution of chloramphenicol base (1d; 0.53 g, 2.5 mmol) in

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(5) Previous attempts to derive hybrid antibiotics from a combination of structural features of chloramphenicol (1a) and puromycin were based on an entirely different rationale and they invariably led to compounds with a marginal or no biological activity: (a) Vince, R.; Almquist, R. G.; Ritter, C. L.; Daluge, S. *Antimicrob. Agents Chemother.* 1975, *8*, 439–443. (b) Verheyden, J. P. H.; Wagner, D.; Moffatt, J. G. *J. Org. Chem.* 1971, *36*, 250–254. For biochemical testing, see ref 1. The *p*-methoxy-L-phenylalanyl analogue of chloramphenicol exhibited some biological activity[5a] but below that of the corresponding glycyl derivative: (c) Coutsogeorgopoulos, C. *Biochim. Biophys. Acta* 1966, *129*, 214–217. Neither the inhibition curves nor K_i values were reported.
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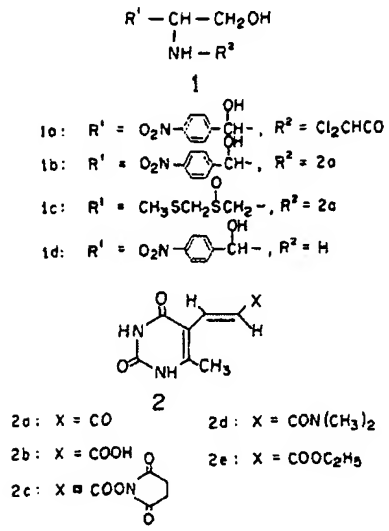

40% aqueous acetonitrile (20 mL) was then added dropwise from a syringe at 0 °C. An almost clear mixture was stirred for 30 min at 0 °C and for 1 h at room temperature. Filtration, evaporation in vacuo, and addition of water (5 mL) gave a crystalline product, **1b** (0.75 g), containing traces of starting materials **1d** and **2b**, as evidenced by TLC[8] (CH_2Cl_2–CH_3OH, 4:1). Further purification on ion-exchange columns of Dowex 50 (pyridinium form) and Dowex 1 (HCO_3^-) with 10% aqueous pyridine as an eluent gave, after crystallization from water, the title compound **1b** (0.34 g, 33%), mp 173–177 °C (transition point);[9] UV max (0.01 M Na_2HPO_4, pH 7) 296 nm (ϵ 28 200), shoulder 275 (25 600), UV max (ethanol) 296 nm (ϵ 28 500), shoulder 270 (24 300); CD max (0.01 M Na_2HPO_4, pH 7) 260 nm ([θ] 26 100), 296 ([θ] −27 200); CD max (ethanol) 255 ([θ] 41 100), 280 ([θ] −32 800), shoulder 300 ([θ] −26 100); NMR[10] (CD_3SOCD_3 + D_2O) δ 8.18 and 7.62 (2 d, 4, *p*-nitrophenyl), 7.13 and 7.02 (2 d, 2, trans-CH=CH), 5.06 (d, 1, CHOH), 3.48 (m, 2, CH_2OH, CHNH overlapped with HDO), 2.26 (s, 3, CH_3). Anal. ($C_{17}H_{18}N_4O_7 \cdot H_2O$) C, H, N.

Sparsophenicol (**1b**) is a strong inhibitor of *N*-acetyl-L-phenylalanylpuromycin formation from *N*-acetyl-L-phenylalanyl tRNA–70S *Escherichia coli* ribosome–poly(U) complex and puromycin.[11] Similar to chloramphenicol[1] (**1a**) and sparsomycin[12] (**1c**), compound **1b** is a competitive inhibitor of puromycin at lower concentrations, but it exhibits an uncompetitive[13] inhibition at higher concentrations[14] (Figure 1). It has to be emphasized that replacement of *N*-acyl groups in **1a** and **1c** with other aromatic or heteroaromatic residues[1,15,16] led invariably to a loss of biological activity. This fact, along with a low inhibition constant ($K_i = 3 \times 10^{-6}$ M),[17] supports the conclusion that the pyrimidineacrylic acid moiety plays an important role in the inhibition of ribosomal peptide synthesis with **1b**, probably binding to the same region of ribosomal peptidyltransferase as in sparsomycin (**1c**). The importance of this portion of the molecule is further underlined by the fact that ester **2c** and amide[18] **2d** are also inhibitors of the puromycin reaction, albeit of lesser potency. Thus, amide **2d**, whose K_i (3.5×10^{-4} M) is close to the K_M of puromycin[19] (2.2×10^{-4} M), exhibits a clear competitive inhibition pattern. The effect of ester **2c** is weaker (ca. 20% inhibition at 3.8×10^{-4} M). Both derivatives are the first biologically active analogues of sparsomycin (**1c**) lacking the D-aminopropanol moiety. Compounds[8] **2b** and **2e** are virtually inactive.

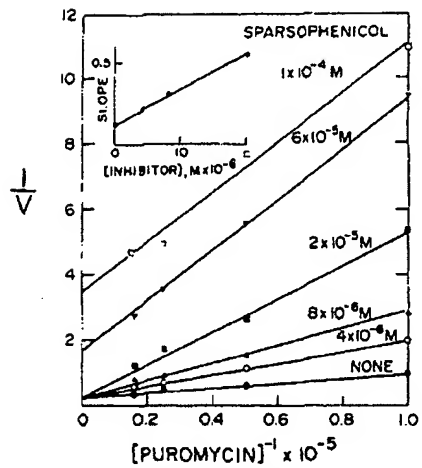

Figure 1. Lineweaver–Burk plot of the effect of sparsophenicol (**1b**) on the rate of *N*-acetyl-L-[^{14}C]phenylalanylpuromycin formation. Inset shows the linear relationship between the slope and inhibitor concentration in the concentration range where the inhibition was competitive. The complex of *N*-acetyl-L-[^{14}C]-phenylalanyl tRNA-70S *E. coli* ribosome–poly(U) was employed in the reaction with puromycin as specified in ref 1.

Although the biological testing has not yet been completed, it is already apparent that sparsophenicol (**1b**) exhibits properties distinctive from both chloramphenicol (**1a**) and sparsomycin (**1c**). Thus, unlike antibiotic **1a**, compound **1b** has virtually no antimicrobial activity as determined in ten different strains, including *E. coli* (minimal inhibitory concentrations were above 100 mg/mL). This strongly indicates that sparsophenicol (**1b**), which is less lipophilic than **1a**, is unable to penetrate the microbial cell membrane. Also, in contrast to sparsomycin (**1c**) and some of its analogues,[16,20] compound **1b** is devoid of in vitro antitumor activity. It did not inhibit the growth of murine leukemia L1210 cells. Whether the latter finding relates to sparsophenicol's inability to penetrate the cell membrane or a lack of response toward the eucaryotic

(8) Precoated TLC sheets, silica gel 60 F_{254}, 6.5 × 2.5 cm (Merck, Darmstadt, Germany), were used.
(9) Determined on a microscopic hot stage (Reichert Thermovar, Austria).
(10) FT 100 instrument; chemical shifts relative to external $(CH_3)_4Si$.
(11) For details on this assay system and the inhibition kinetics, see ref 1 and references therein.
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(14) Deviations from a competitive pattern were also observed at higher concentrations of chloramphenicol (**1a**): Pestka, S. *J. Biol. Chem.* 1972, *247*, 4669–4678.
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(17) The K_i values of chloramphenicol (**1a**)[1] and sparsomycin (**2a**)[12] measured in a similar assay were 1.6×10^{-6} and 0.5×10^{-6} M, respectively.
(18) The syntheses of these materials will be described elsewhere.
(19) Li, C.; Bhuta, P.; Žemlička, J. *Biochemistry* 1978, *17*, 2537–2545.
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peptidyltransferase target remains to be determined.

UV spectra of **1b** in aqueous solution (pH 7) and ethanol are almost superimposable, which indicates a lack of effective interaction (stacking) between both aromatic portions.[21] Similar conclusions can also be drawn from CD spectra showing a greater molecular ellipticity in ethanol than in water. It is, therefore, likely that the conformation of **1b** is "extended" as found, e.g., in puromycin.[22] Further biological testing of **1b**, along with the synthesis of additional hybrid antibiotics, is the subject of our present investigation.

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(21) In systems that are extensively stacked in aqueous solutions, as evidenced by hypochromism, a considerable destacking, and, hence, an increase of extinction coefficient, occurs in ethanol: (a) Browne, D. T.; Eisinger, J.; Leonard, N. *J. J. Am. Chem. Soc.* **1968**, *90*, 7302–7323.

(22) Sundaralingam, M.; Arora, S. K. *J. Mol. Biol.* **1972**, *71*, 49–70.

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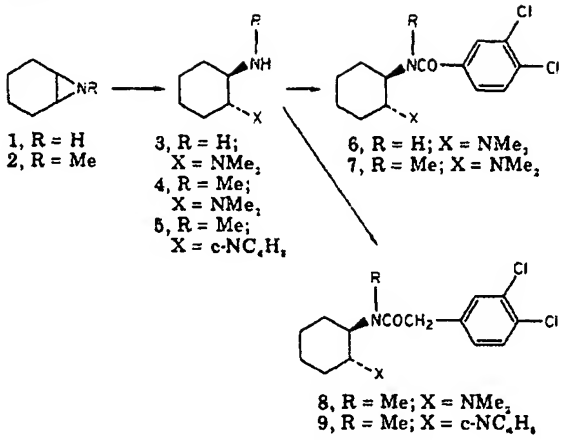
Benzeneacetamide Amines: Structurally Novel Non-mμ Opioids

Sir:

Studies with endorphins[1,2] and benzomorphans[3] have led to the hypothesis of multiple opioid receptors. The understanding of the functional significance of particularly the non-mμ (non-morphine receptive) receptors has been hampered by the scarcity of selective agonists and antagonists. We report here the prototype of a new series of opioid analgesics that does not have other morphine-like or narcotic antagonist effects. We also highlight the close structural similarity of this compound to compounds with potent mμ properties.

We have recently described our work with cycloalkane-1,2-diamines which led to potent antidepressant-like agents.[4] Inclusion of the benzamide and benzeneacetamide structural moieties in the *trans*-cyclohexane-1,2-diamine class of compounds led us to the discovery of a novel class of analgesics.

Scheme I



1, R = H
2, R = Me

3, R = H; X = NMe_2
4, R = Me; X = NMe_2
5, R = Me; X = c-NC_4H_8

6, R = H; X = NMe_2
7, R = Me; X = NMe_2

8, R = Me; X = NMe_2
9, R = Me; X = c-NC_4H_8

The structures and results of biological testing[5] in Table I briefly summarize the evolution of the structure–activity relationships (SAR) of this series. In mice, the benzamide **6** was discovered to have morphine-like analgesic and behavioral properties but lower potency than morphine. Methylation of the amide nitrogen afforded compound **7** and resulted in a considerable increase in analgesic potency but retention of morphine-like behavioral properties. The benzeneacetamide analogues (**8** and **9**), however, displayed no such behavioral effects but retained analgesic properties. In this regard, the pyrrolidine (**9**) is somewhat more potent subcutaneously than the dimethylamino comopund **8** and much more potent orally (tail-flick ED_{50} = 16 and >100 mg/kg, respectively). The apparent analgesic properties of these novel compounds are not the result of motor incapacitation, since the analgesic ED_{50}'s are well divorced from the gross sedative (inclined screen) ED_{50}. None of these compounds displayed morphine antagonist activity.

Further studies with **9** indicate that despite lacking mμ behavioral properties (Straub tail, arched back and increased locomotor activity), it is an opioid analgesic as defined by antagonism by the opioid antagonist naloxone. For example, 0.8 mg/kg of naloxone hydrochloride blocks the tail-flick analgesic effect of 25 mg/kg of **9**. Extensive biological evaluation[6] has confirmed the non-mμ opioid nature of **9** and suggested that it is a highly selective agonist for the so-called κ opioid receptor. As a structurally novel nonpeptide agonist, this compound may be a useful tool for delineating the functions of κ receptors. The close structural similarity of **8** and **9** to a potent mμ agonist (**7**) also offers the opportunity to understand the different steric requirements of these subpopulations of opioid receptors. Lastly, the benzeneacetamide amines may prove to be useful analgesics lacking many of the undesirable properties of morphine and the benzomorphans. This is

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